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RESEARCH ARTICLE

Pharmacokinetics, druglikeness and anti-asthmatic potential of 6-dehydrogingerdione via modulation of β_2-adrenergic receptor

C. Lalrinmawia, C. Biakthansanga, Ricky Lalruatfela, B. Lalruatfela*

Department of Zoology and Department of Life Sciences, Pachhunga University College, Mizoram University, Aizawl-796001, Mizoram, India

Asthma is a common chronic disease infecting the lower airway resulting in cough, chest constriction and wheezing. Treatment of asthma includes drugs such as salbutamol, levalbuterol, metaproterenol and terbutaline as these can cause relaxation of the muscles of the windpipe. One of the most common spices that is enriched with numerous medicinal properties is ginger, which is reported to have anti-inflammatory, antidiabetic, antiemetic, anticancer and anti-obesity properties. In this paper we analyse the pharmacokinetics, druglikeness and binding affinity of 6-dehydrogingerdione (6-DG) to β_2-adrenergic receptor (ADRB2) using in silico approach. We observe that 6-DG fulfilled druglikeness tests and may be safe for human consumption and also exhibited a strong binding affinity to ADRB2 which is comparable to the standard asthma drug salbutamol. The amino acids involved in the interaction of 6-DG and salbutamol to ADRB2 differ only by one residue. We concluded that further in vitro and in vivo analyses are required to confirm the potential of 6-DG as an anti-asthmatic medication.

Keywords : 6-dehydrogingerdione, Asthma, Anti-asthma, β_2-adrenergic receptor;

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*For correspondence:
blalruatfela@pucollege.edu.in

Contact us:
sciencevision@outlook.com

Introduction

Asthma is a common chronic disease infecting the lower airway that can cause physiological complications in humans, like blistering of the airway and production of excessive mucus which both develop complications in air inhalation.[1,2] Signs and symptoms of asthma comprise cough, chest constriction and wheezing. Asthma can be triggered by allergies, respiratory infections, stress, exercise and even medications.[3] Medical treatment of asthma is of two types: one is a type of medicine that can expand the windpipe. Examples of such include β_2-adrenergic receptor (ADRB2) agonists such as salbutamol (albuterol) which are mainly used as inhaler or nebulizer but oral forms and injections are also available. The other type is medications that can remove inflammation of the windpipe and include glucocorticoid steroids. These are also most commonly used as inhalers although injections are also available. Sodium cromoglycate, levalbuterol, metaproterenol and terbutaline are also used for the treatment of asthma.[4]

Ginger (*Zingiber officinale* Roscoe) is a versatile herb native to India or Southeast Asia consumed as food and as traditional medicine. The tuber of ginger has been reported to possess antibacterial, antioxidant, antidiabetic, anti-obesity, neuroprotective, anticancer, antinausea, antipyretic, and anti-inflammatory properties.[5] It has been reported to be used for the treatment of gastric irritation and also contains vitamins A, C and E and many other nutrients.[6] Studies have shown that 6-gingerol, one of the chemical compounds of ginger can inhibit cancer, especially lung, skin and urinary tract cancers.[7] Ginger is known to be high in

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phenolic compounds and contains terpenes, polysaccharides, lipids, organic acids, and raw fibres, among other things. The health advantages of ginger are linked mostly to its phenolic components, such as gingerols and shogaols. Further, β-bisabolene, α-curcumene, zingiberene, α-farnesene, and β-sesquiphellandrene are terpene components present in ginger. Another significant component of ginger is 6-dehydrogingerdione (6-DG) which is reported to have therapeutic properties including antitumor and anti-atherosclerotic properties.[8] It has also been shown to modulate the immune system by inhibiting the production of pro-inflammatory molecules, such as cytokines and enzymes, thereby reducing inflammation in the body.[9]

Investigation of natural compounds for the treatment of human and livestock diseases have led to important discoveries in pharmacological and veterinary sciences. Drug discovery is a process that explores the diverse biological and synthetic compounds for their medicinal properties and developed them into effective drugs. Despite its critical utility, drug discovery encounters enormous hindrances because the traditional ways of drug development rely on trial-and-error methods which are usually expensive, time-consuming, limiting in throughput and stunted in accuracy.[10] The National Organization for Rare Disorders has estimated about 7000 types of rare diseases out of which only a few percent of them have pharmacological treatment. Yet, 10% of the world's population is affected by these rare diseases. So, to counter such impediments, in silico approaches have paved their way into pharmacological research by providing fast computational processes and virtual high-throughput screenings.[11,12]

In this study, we analyze the pharmacokinetic, druglikeness and molecular docking affinities of 6-DG to ADRB2 for its potential use as a treatment for asthma.

Methodology

Pharmacokinetics and druglikeness: Pharmacokinetic parameters such as absorption, distribution, metabolism, excretion, and toxicity (ADMET) of 6-DG were analysed using pkCSM (https://biosig.lab.uq.edu.au/pkCSM/) where isomeric SMILE of 6-DG obtained from PubChem (Compound CID: 9796015) (https://pubchem.ncbi.nlm.nih.gov/) was utilised for the tests. The isomeric SMILE of the compound was also used for analysing the druglikeness with SwissADME analytical platform (http://www.swissadme.ch/).

Retrieval of ligand and receptor: The structures of 6-DG and salbutamol (Compound CID: 2083) retrieved from PubChem were processed in Chem Bio 3D Ultra 12.0 software. Minimization of energy were performed on the compounds and the documents were saved in protein data bank (PDB) format for further preparation for molecular docking. The receptor β_2-adrenergic receptor (ADRB2) (6KR8) was retrieved and downloaded in PDB format from RCSB database (https://www.rcsb.org/) and processed with Molegro Molecular Viewer software. Undesired molecules were eliminated from the receptor and the molecules were exported in PDB format. Salbutamol is used as a positive control for molecular docking.

Molecular docking: After the addition of polar hydrogen and Kollman charges to the receptor using AutoDock software, the receptor was exported in PDBQT file. The ligand was also processed for molecular docking and exported in PDBQT file. Grid box was prepared with Angstrom set to 1 and coordinates of x= 44, y= 94, z= 66 and center x= -31.221, y= 35.341, z= 13.825. Molecular docking was performed for 6-DG and salbutamol separately on ADRB2 using Auto Dock Vina platform with an exhaustiveness of 8. The results were saved for further visual analyses.

Visualization of results: BIOVIA Discovery Studio Visualizer 2016 v16.1.0.15350 was used for visualization of the molecular docking results.

Results

The water solubility of 6-DG is found to be -3.48 log mol/L and Caco-2 permeability is -0.913 log

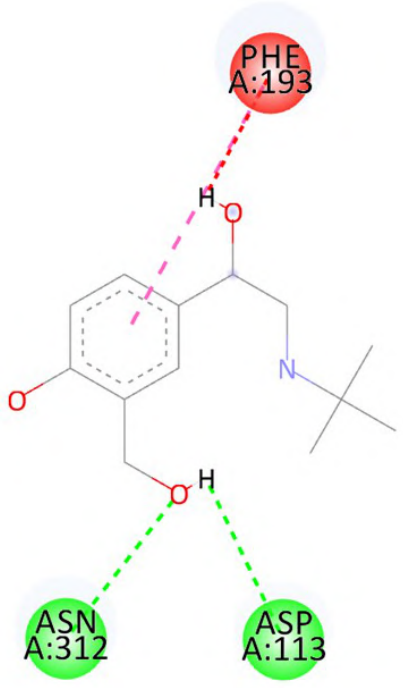

Figure 1: Interaction of salbutamol and β2-adrenergic receptor (ADRB2) showing interacting amino acid residues

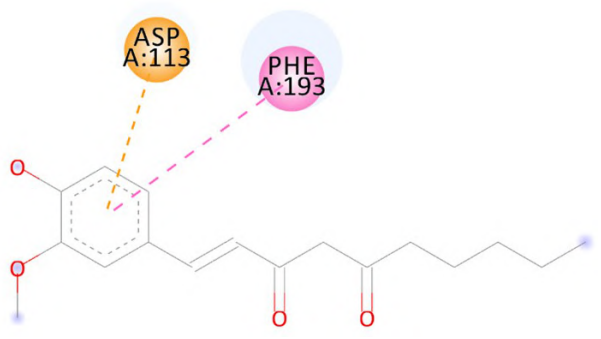

Figure 2: Interaction of 6-dehydrogingerdione (6-DG) and β_2-adrenergic receptor (ADRB2) showing interacting amino acid residues

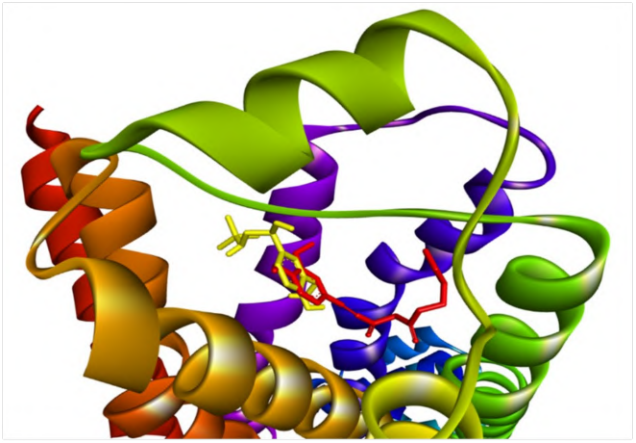

Figure 3: 6-dehydrogingerdione (red) and salbutamol (yellow) occupying similar binding site on β_2-adrenergic receptor

Papp. The intestinal absorption in human is 93.152% and skin permeability is -2.789 log Kp. The compound is predicted to be a P-glycoprotein I inhibitor but not inhibitor of P-glycoprotein II. It has also been predicted not to be a substrate of P-glycoprotein. 6-DG does not have cytochrome P450 2D6 (CYP2D6) substrate while cytochrome P450 3A4 (CYP3A4) substrate is present. The compound is also predicted to be an inhibitor of cytochrome P45 due to the presence of CYP1A2 inhibitor and CYP2C19 inhibitor. On the other hand, CYP2C9 inhibitor, CYP2D6 inhibitor and CYP3A4 inhibitor are absent. The total clearance of the compound is predicted to be 0.306 log ml/min/kg. In addition, the compound is capable of acting as Renal Organic Citation Transporter 2 (Renal OCT2). Computational AMES test showed that the compound is not likely to be AMES positive and hence is not mutagenic. The maximum tolerated dose in human is found to be 0.662 log mg/kg/day. The compound is also not

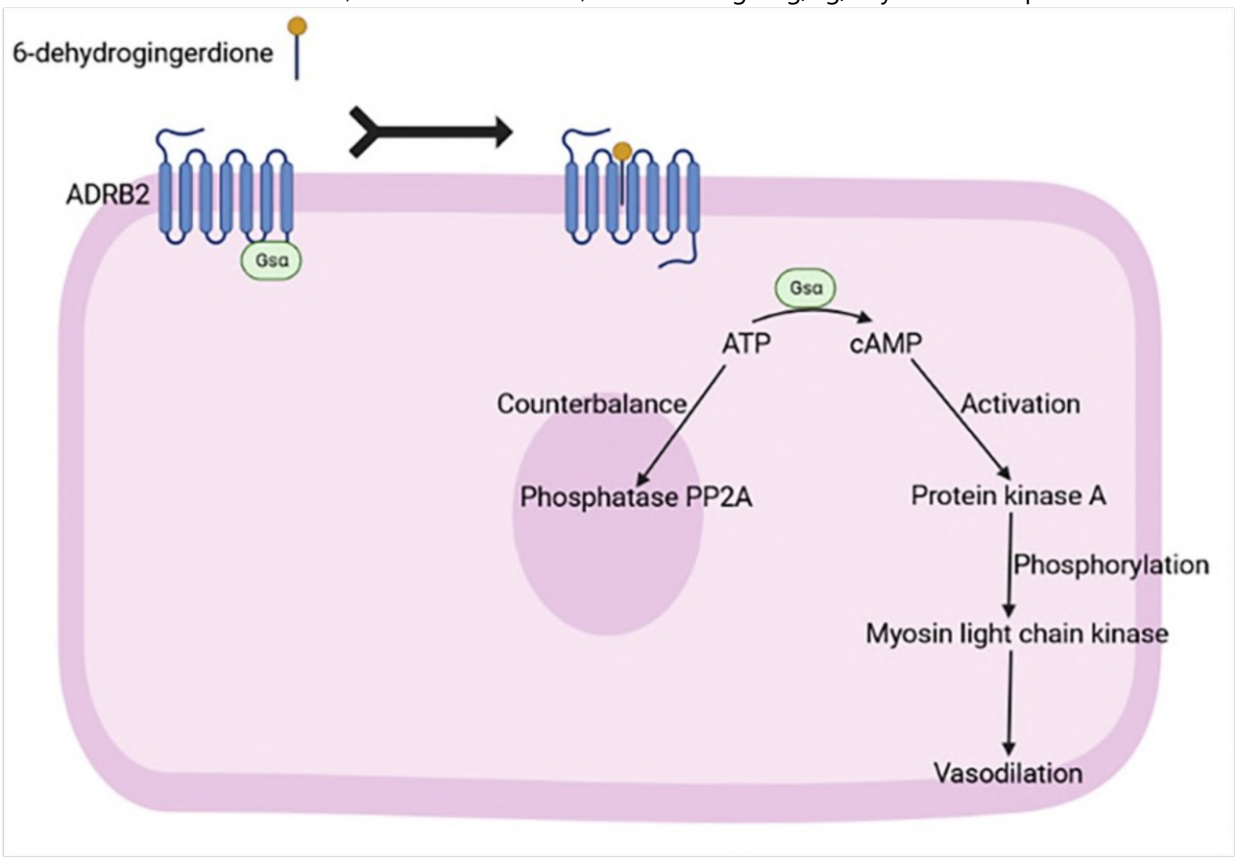

Figure 3: Probable molecular mechanism of 6-dehydrogingerdione action via activation of ADRB2 present in epithelial cells of the airway

likely to be hERG I and hERG II inhibitor. The Oral Rat Acute Toxicity (LD_{50}) of the compound is 1.945 mol/kg while the Oral Rat Chronic Toxicity (LOAEL) is 1.937 log mg/kg. The compound has a negative result for skin sensitisation and hepatoxicity. The result for Tetrahymena pyriformis toxicity is 1.819 log ug/L and the Minnow toxicity is 0.241 log mM. Druglikeness studies showed that the compound satisfied all the criteria such as Lipinski's rule of five, the Ghost's rule, Veber's rule, Egan's rule and Muegge Rule and has a bioavailability of 0.55%.

Molecular docking analysis showed that salbutamol and ADRB2 interacted with a docking score of -6.6 kcal/mol and interacted with amino acids such as aspartic acid (position: 113), phenylalanine (position: 193) and asparagine (position: 312) (Figure 1). The molecular docking score of 6-DG to ADRB2 is -7.1 kcal/mol and this interaction involves amino acids such as aspartic acid (position: 113) and phenylalanine (position: 193) (Figure 2). It was also observed that salbutamol and 6-DG occupy similar positions on ADRB2 (Figure 3)

Discussion

The health benefits of ginger have been extensively studied, however, many of the biological effects of the compounds of ginger is yet to be explored. Ginger has been traditionally used for the treatment of food poisoning and as an anti-allergic.[13,14] Some of the compounds of ginger including 6-DG have been reported to have anti-inflammatory, antiallergic, antitumor and antiatherosclerotic properties.[8,15] *Tetragonula* sp., which contains 6-DG, showed anti-inflammatory effects in rat's paw inflammation model.[16] 6-DG isolated from ginger was also reported to have anti-larval activity against *Aedes aegypti* L. and *Culex quinquefasciatus* Say.[17] 6-DG also has anthelmintic effect against *Hymenolepis nana*.[18] The anti-diabetic property of 6-DG analysed showed that the mechanism of action is possibly by stimulating the secretion of insulin via closure of KATP channels in pancreatic β-cells.[19]

Compounds of ginger including 6-DG have antioxidant effects that contribute to antimicrobial activity against extensively drug-resistant *Acinetobacter baumannii*.[20] In neuron-like rat pheochromocytoma cell line, 6-DG showed free radical scavenging activity and also protects against oxidative stress-induced neuronal damage.[21] 6-DG also exhibited a protective effect against lipid peroxidation in a manner comparable to curcumin.[22] In human breast cancer cell lines, 6-DG arrested the cell cycle at G2/M phase and also induce apoptosis.[23] 6-DG induced apoptosis via Fas receptor, p53-regulated DR5 expression and ROS-dependent pathways.[24] 6-DG has also been shown to induce the production of transforming growth factor-B (TGF-B), vascular endothelial growth factors (VEGF) and platelet-derived growth factor-AB (PDGF-AB) and eventually increased fibroblast collagen production and also reduce expression of matrix metalloproteinase-1. 6-DG is also reported to suppress c-Jun and extracellular signal-regulated

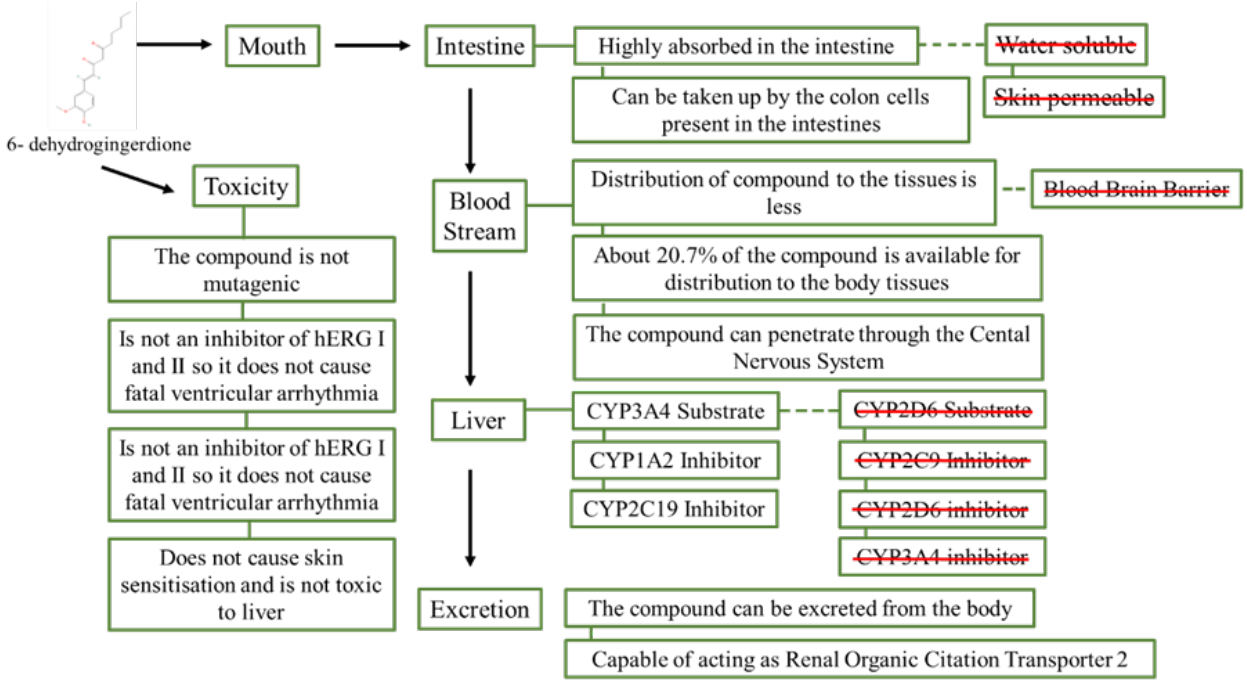

Figure 3: Pharmacokinetic model of 6-dehydrogingerdione

kinases phosphorylation in fibroblasts.[25]

ADRB2 is a receptor responsible for many important physiological functions reported to be involved in the relaxation of smooth muscles in the airway, gastrointestinal tract, urinogenital ducts and seminal tract.[26] It has been the target of short-acting ADRB2 agonists such as salbutamol, levalbuterol, metaproterenol and terbutaline in the treatment of asthma, COPD or emphysema.[27] Our study shows 6-DG and salbutamol binds to a similar binding region on ADRB2 (Figure 4) even though the amino acids involved in the interaction are not all similar (Figure 1 & 2). 6-DG exhibited lower binding affinity than salbutamol to ADRB2 which may infer that 6-DG may be employed as an agonist of ADRB2 in relaxing bronchial tract during asthma attack. It is worth noting that the amino acids involved in the binding of 6-DG or salbutamol to ADRB2 differ only by one amino acid residue, which is asparagine at position 312. Since the interactions of the two compounds with ADRB2 are in a way comparable, 6-DG may induce a similar effect like salbutamol in the modulation of ADRB2. The binding of 6-DG on the receptor may result in the activation of adenyl cyclase by Gsα which may further catalyse the production of cyclic adenosine monophosphate (cAMP). This may activate protein kinase A (PKA) and counterbalance protein phosphatase 2A (PP2A). Phosphorylation of myosin light-chain kinase by PKA may then result in vasodilation and eventual relaxation of the airway in asthma (Figure 4).[28] The pharmacokinetic and druglikeness results depicted that 6-DG is consumable as drug (Figure 5). However, further in vitro and in vivo analyses are required to confirm our results.

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